The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

# *Variant: NM_000527.5(LDLR):c.269A>C (p.Asp90Ala)*

Version: 1.0

*CA404075695*

*440555 (ClinVar)*

**Gene**: LDLR (HGNC:3949)
**Condition**: hypercholesterolemia, familial (MONDO:0007750)
**Inheritance Mode**: Semidominant inheritance
**UUID:** 484e1059-d6ac-4816-9757-dbdb0ed3bed2
**Approved on**: 2022/8/28
**Published on**: 2022/8/28

## *HGVS expressions*

**NM_000527.5:c.269A>C**
**NM_000527.5(LDLR):c.269A>C (p.Asp90Ala)**
NC_000019.10:g.11102742A>C
CM000681.2:g.11102742A>C
NC_000019.9:g.11213418A>C
CM000681.1:g.11213418A>C
NC_000019.8:g.11074418A>C
NG_009060.1:g.18362A>C
ENST00000252444.10:c.527A>C
ENST00000559340.2:c.269A>C
ENST00000560467.2:c.269A>C
ENST00000558518.6:c.269A>C
ENST00000252444.9:c.523A>C
ENST00000455727.6:c.269A>C
ENST00000535915.5:c.190+2397A>C
ENST00000545707.5:c.269A>C
ENST00000557933.5:c.269A>C
ENST00000557958.1:n.355A>C
ENST00000558013.5:c.269A>C
ENST00000558518.5:c.269A>C
NM_000527.4:c.269A>C
NM_001195798.1:c.269A>C
NM_001195799.1:c.190+2397A>C
NM_001195800.1:c.269A>C
NM_001195803.1:c.269A>C
NM_001195798.2:c.269A>C
NM_001195799.2:c.190+2397A>C
NM_001195800.2:c.269A>C
NM_001195803.2:c.269A>C

**Likely Pathogenic**

**Met criteria codes** 4

PP3 PP4 PM5_Strong PM2

**Not Met criteria codes** 22

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PP1 PP2 PM6 PM1 PM3
PM4 BA1 BS2 PVS1 BS1
BS4 BS3 BP5 BP7 BP4 BP3
BP1 BP2 PS1 PS2 PS3 PS4

Evidence Links 0

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Familial Hypercholesterolemia VCEP***

**The NM_000527.5(LDLR):c.269A>C (p.Asp90Ala) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM5_Strong, PM2, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (https://doi.org/10.1101/2021.03.17.21252755). The supporting evidence is as follows: PM5_Strong - 4 other missense variants is the same codon: - NM_000527.5(LDLR):c.268G>A (p.Asp90Asn) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.268G>T (p.Asp90Tyr) - classified as Likely pathogenic by the FH VCEP, with these guidelines - NM_000527.5(LDLR):c.269A>G (p.Asp90Gly) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.270T>A (p.Asp90Glu) - Pathogenic by these guidelines There are 3 variants classified as Pathogenic by these guidelines, so PM5_Strong is met. PM2 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met. PP3 - REVEL = 0.964. It is above 0.75, so PP3 is met PP4 - Variant meets PM2, and was identified in 1 index case with SB criteria for FH (The clinical diagnosis of hoFH was confirmed on the basis of total cholesterol >500 mg/dl at the time of diagnosis, the presence of xanthomas at an early age, and the presence of primary hypercholesterolemia in the probands' parents or other first degree relatives. This case had total cholesterol 840mg/dl at 3 years of age) from PMID 19026292 (Kolansky et al., 2008), USA so PP4 is met**

**Met criteria codes**

| | | |
|---|---|---|
| **PP3** | ✔ | REVEL = 0.964. It is above 0.75, so PP3 is met |
| **PP4** | ✔ | Variant meets PM2, and was identified in: - 1 index case with SB criteria for FH (The clinical diagnosis of hoFH was confirmed on the basis of total cholesterol >500 mg/dl at the time of diagnosis, the presence of xanthomas at an early age, and the presence of primary hypercholesterolemia in the probands' parents or other firstdegree relatives. This case had total cholesterol 840mg/dl at 3 years of age) from PMID 19026292 (Kolansky et al., 2008), USA so PP4 is met |
| **PM5_Strong** | ✔ | 4 other missense variants is the same codon: - NM_000527.5(LDLR):c.268G>A (p.Asp90Asn) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.268G>T (p.Asp90Tyr) - classified as Likely pathogenic by the FH VCEP, with these guidelines - NM_000527.5(LDLR):c.269A>G (p.Asp90Gly) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.270T>A (p.Asp90Glu) - Pathogenic by these guidelines There are 3 variants classified as Pathogenic by these guidelines, so PM5_Strong is met. |
| **PM2** | ✔ | This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PP1** | ✖ | no case data |
| **PP2** | ✖ | not applicable |

| | | |
|---|---|---|
| **PM6** | ✖ | no case data |
| **PM1** | ✖ | Variant is not in exon 4 and does not alter Cys, so not met |
| **PM3** | ✖ | Variant meets PM2, but there are no case data |
| **PM4** | ✖ | variant is missense, so not met |
| **BA1** | ✖ | This variant is absent from gnomAD (gnomAD v2.1.1), so not met |
| **BS2** | ✖ | no case data |
| **PVS1** | ✖ | variant is missense and not in initiation codon, so not met |
| **BS1** | ✖ | This variant is absent from gnomAD (gnomAD v2.1.1), so not met |
| **BS4** | ✖ | no case data |
| **BS3** | ✖ | no functional study performed |
| **BP5** | ✖ | not applicable |
| **BP7** | ✖ | variant is missense, so not met |
| **BP4** | ✖ | REVEL = 0.964. It is not below 0.50, so not met |
| **BP3** | ✖ | not applicable |
| **BP1** | ✖ | not applicable |
| **BP2** | ✖ | no case data |
| **PS1** | ✖ | no other variant leads to the same amino acid change in the same codon, so not met |
| **PS2** | ✖ | no case data |
| **PS3** | ✖ | no functional study performed |
| **PS4** | ✖ | Variant meets PM2, and was identified in: - 1 index case with SB criteria for FH (The clinical diagnosis of hoFH was confirmed on the basis of total cholesterol >500 mg/dl at the time of diagnosis, the presence of xanthomas at an |

early age, and the presence of primary hypercholesterolemia in the probands' parents or other firstdegree relatives. This case had total cholesterol 840mg/dl at 3 years of age) from PMID 19026292 (Kolansky et al., 2008), USA not enough, so not met

## Curation History

owing 1 to 1 of 1 rows

| ee Report | Preferred Variant Title | Classification | Condition | Published Date | Version | Criteria Specification | Gene |
|---|---|---|---|---|---|---|---|
| View | NM_000527.5(LDLR):c.269A>C (p.Asp9... | Likely Pathogenic | Hypercholesterolemia, Familial | 2022-08-28 | 1.0 | - | LDLR |

owing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.